with said disease, the form consisting essentially of:

an effective amount for suppressing said response of a bystander antigen; and

a pharmaceutically acceptable carrier or diluent;

H3 wherein said bystander antigen is not insulin nor an antigen to which T cells that mediate said disease in said host are sensitized, and wherein said dosage form is contained in an inhaler or nebulizer, and wherein said bystander antigen is specified to an organ or tissue afflicted by immune attack during said disease.

56. (Amended) The pharmaceutical dosage form of claim 48 wherein said

H4 disease is selected from the group consisting of Type I diabetes and animal models therefor and said bystander antigen is glucagon.

REMARKS

Reconsideration is respectfully requested. Claims 38 and 49 have been canceled and claims 37, 46, 48 and 56 have been amended without prejudice or admission. A Marked-Up copy of this amendment is attached as Exhibit I. Thus, claims 37-38, 42-44, 46, 48, 52-54, 56-57 are now pending.

Claim 37 has been amended to make it even more clear that prevention is not included. The claim requires explicitly that the autoimmune response be ongoing at the time of the treatment. Claim 37 has also been amended to make clear that the T cells that have

not been sensitized are the T cells of the host being treated, and to incorporate the limitations of canceled claim 38 (except that instead of "specific" in claim 38, the present claim 37 recites "present").

Claims 38 and 49 have been canceled without prejudice or disclaimer. Claim 46 has been made independent. Claim 48 has been amended to track the amendments to claim 37, and claim 56 was amended to correct an obvious typographical error. Thus, no new matter is introduced by these amendments. Entry and consideration of these amendments is therefore respectfully requested.

I. Rejection of Claims under 35 U.S.C. § 112, First Paragraph

This rejection is respectfully traversed.

Scope of the Claims

The Examiner is of the opinion that the claims were broadened by deleting the phrase "not an autoantigen". In fact, this phrase was replaced by its definition, hence there has been no broadening of the scope of the claims.

The Examiner is also of the opinion that the claims encompass prevention of an autoimmune response. This is not so, as made clear by the present amendment which requires the autoimmune response to be ongoing.

Hence, to the extent that the rejection was based on the alleged broadening of the claims and the alleged prevention of autoimmune response, this rejection should be withdrawn.

The Examiner's suggested amendment that the claims should be limited to subjects having the autoimmune disease was taken into consideration, but it was not adopted because it is possible for a subject to have an ongoing abnormal autoimmune response before developing overt symptoms of the autoimmune disease. Applicants are not claiming prevention of an autoimmune response nor prevention of a disease because the claims only require suppression of an autoimmune response and not elimination.

Thus the claims are directed to "treating...by suppressing an ongoing autoimmune response" not to "treating an autoimmune disease".

PLP/MBP Autoantigens or Bystanders?

The Examiner is of the opinion that PLP and MBP are autoantigens in humans. But, what is an autoantigen for one human being is not necessarily an autoantigen for another human being. The Examiner has not shown that all human beings with an ongoing autoimmune response associated with multiple sclerosis have activated T cells that recognize PLP. The Cohen reference does not stand for that proposition. The Cohen reference states only that immunizing mice with PLP induces disease. This is far from establishing that PLP would necessarily be an antigen to which the activated T cells of a particular host are sensitized. In other words, in the EAE model, administering an autoantigen means administering the same substance used to induce disease, which by definition is the antigen to which the activated T cells of the host are sensitized. If another antigen is administered, it is not an autoantigen. The Cohen reference explicitly states:

the encephalitogeneity of MBP or PLP peptides is dependent on the expression of certain H-2 antigens of mouse strains"

Hence, in mice that do not express the requisite H-2 antigens for PLP, PLP will not be an autoantigen. Analogously, this can be applied to humans. Also, the Examiner maintains that the experiment with PLP and MBP does not suffice for the human. But the Examiner has no basis for this assertion. The Hafler paper (J. Immunology, 139:68, 1987) does not state that all MS patients have activated T cells to PLP. To the contrary, Hafler et al. also supports the applicants' position because they identified individuals in which neither peripheral nor CNS T cells recognized PLP. The comments of the authors' at the right-hand column on page 71 of that reference are merely speculation.

Applicants point out that the principle of the present invention has been dramatically illustrated in the specification. Applicants have also given a list of antigens which are putative bystanders. The T cells of a subject may or may not be activated against them. See Table 1. The T cells of the host must be tested for activation and responsiveness to antigen. Thus it is not true that there are no examples that would be appropriate for humans. It is of course possible that no one antigen will be appropriate for all humans.

Lastly, turning to the OVA experiment, the Examiner's comments are not understood. The Examiner's attention is drawn to the OVA *in vivo* experiments at page 43, lines 33-44; page 44, lines 1-35, page 45, lines 1-9; and Figures 6A-6C, 7, 8 and 9 of the application. This portion of the specification describes how feeding OVA to rats suppresses DTH responses in the footpad caused by immunization with MBP/CFA, provided that OVA was injected subcutaneously in the same footpad. In order to emulate a bystander antigen

(OVA) specific to the afflicted tissue (footpad) applicants injected OVA in the afflicted footpad after the immunization had taken place.

With respect to Example 3, applicants said only that it teaches how to identify bystanders. That experiment shows only that regulatory T cells raised by feeding a certain antigen (MBP) suppress responses of an OVA spleen cell line. In that experiment, the OVA cell line is a responder. This experiment shows that the suppression is non-specific even though the T cells from fed (i.e., tolerized) animals are specific to the fed antigen. This illustrates the broad applicability of the present invention.

The Examiner is invited to call the undersigned to go through Example 3 and its meaning, because there is a misunderstanding here. The cells from MBP-fed animals are capable of suppressing proliferation of an OVA responder cell line. This means that the cells from tolerized animals which recognize MBP (used to tolerize the animals) secrete something that penetrates to the lower well. That something suppresses cells specific to OVA, not only cells specific to MBP. When the OVA cell line is exposed to OVA (after the something from the upper well has been secreted by the tolerized MBP-specific cells) it does not proliferate. Hence, the suppression is nonspecific and is independent of the antigen that the responder cells recognize.

Conversely, when the modulator cells are OVA-fed cells (which recognize OVA) they secrete "something" into the lower well which causes the responder MBP-cell line (which should proliferate when MBP is added) to not proliferate. This also illustrates that the suppression mediated by T cells from animals tolerized with an antigen is not specific to T

cells that are activated by the same antigen, but extends to suppress proliferation of T cells that recognize an entirely different antigen.

So while the T cells that mediate the suppression do so upon encountering the (fed) antigen which elicited them, the suppression is effective against activated T cells of entirely different specificities. Thus, the cells mediating the suppression are specific to the bystander antigen used to elicit them, but the cells suppressed need not be.

As stated before, and as testified to by Dr. von Herrath, Tisch is directed solely to use of one antigen, an autoantigen, to suppress autoimmune response and not to bystander suppression. Tisch does not use the term bystander suppression nor does he have the concept. The concept originated with the present inventors. Tisch's review preceded publication of the work of the present inventors and therefore cannot be used as a criticism of it. To the contrary, the concept of bystander suppression responds to Tisch's criticism by showing that a fed antigen can suppress responses to another antigen.

It is because of this demonstrated general applicability of bystander suppression that applicants are able to claim broadly.

II. The Provisional Rejections

A terminal disclaimer is enclosed without admission as to whether the present claims are or are not patentable over those of the related applications, but only as an expedient to prosecution.

IV. Allowable Subject Matter

Claim 46, limited to the use of glucagon, is now in independent form. It is submitted that it is allowable.

V. Conclusion

Reconsideration is respectfully requested in light of the foregoing amendments and remarks. Favorable action is respectfully solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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